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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner: CHANNAVAJJALA, L Art Unit: 1615

In re: Application of: Ronald B. MILLER, *et al.*

Serial No.: 10/067,451

Filed: February 5, 2002

For: **PHARMACEUTICAL FORMULATION**

RESPONSE UNDER 37 C.F.R. § 1.111

Assistant Commissioner for Patents
Washington, D.C. 20231

April 17, 2003

Sir:

This communication is in response to the Office Action mailed October 18, 2002, for the above referenced patent application.

REMARKS

Claims 1-8, 11 and 12-25 are pending. Applicants respectfully request reconsideration of the application based on the following remarks.

I. REJECTIONS UNDER 25 U.S.C. § 112, FIRST PARAGRAPH:

A. WRITTEN DESCRIPTION REJECTION:

In the Office Action, claims 1-5, 8, 11, 12, 15, 17 and 22-25 were rejected under 35 U.S.C. § 112, first paragraph on the grounds of lacking of written description. The Examiner stated that "the limitation 'pharmaceutically active ingredient having a solubility in water of greater than 1gm in 250ml water', is very broad and includes any water soluble active ingredient known to date and even extends to any ingredient that would be discovered in [the] future . . ." The Examiner further states that "[i]nstant disclosure only mentions hydromorphone

hydrochloride, diamorphone hydrochloride, tramadol hydrochloride and dihydrocodeine tartarate, as water soluble drugs that are suitable for the instant formulation. There is insufficient written descriptive support for the generic limitation as it includes any undisclosed active agents that fall under the above category." It appears that the Examiner is taking the position that the written description has not been satisfied for the claimed genus of active compounds as it encompasses undisclosed active agents.

This rejection is respectfully traversed. It is pointed out to the Examiner that "[a] specification may, within the meaning of 35 U.S.C. § 112, first paragraph, contain a written description of a broadly claimed invention without describing all species that a claim encompasses." *Utter v. Hiraga*, 6 U.S.P.Q. 2d 1714. It is further pointed out to the Examiner that in order to satisfy the written description requirement for generic claims involving chemical materials, the generic formula should indicate with specificity what the generic claims cover so that one skilled in the art can identify many of the species that the claims encompass. *University of California v. Eli Lilly and Co.*, 43 U.S.P.Q. 1398.

It is respectfully submitted that the originally filed specification and claims of the present invention provide written description for the term "a pharmaceutically active ingredient having a solubility in water of greater than 1gm in 250ml water" as recited in the claims of the present invention. For example, the Examiner is directed to page 2, paragraph 4 which teaches:

> *According to the present invention there is provided a solid, oral, controlled release pharmaceutical dosage form which comprises a pharmaceutically active ingredient having a solubility in water greater than 1gm in 250ml water at 25°C . . .*

The specification further teaches the following at page 3, paragraph 5:

Although morphine and pharmaceutically acceptable morphine salts have been mentioned above as preferred active ingredients, other suitable water soluble active ingredients including hydromorphone hydrochloride, diamorphine hydrochloride, tramadol hydrochloride and dihydrocodeine tartrate.

As demonstrated above, the specification of the present invention contains a description of the genus recited in the claims. The specification further teaches certain active agents which are encompassed by the disclosed genus. As it has been established that there is not a requirement to disclose all species which are encompassed by a genus, it is submitted that there is sufficient written description for the disclosed genus.

Further, it is submitted that a determination of the solubility of an active agent is well within the skill of a pharmaceutical artisan. Accordingly, the disclosed genus of "a pharmaceutically active ingredient having a solubility in water greater than 1gm in 250ml water at 25°C" clearly sets forth the specificity necessary for a skilled artisan to ascertain if a compound falls within the claimed genus.

In view of the above, the Examiner is requested to remove the rejections under 35 U.S.C. § 112, first paragraph on the grounds that the claims lack written description.

B. <u>ENABLEMENT REJECTION:</u>

In the Office Action, the Examiner rejected claims 1-5, 8, 11, 12, 15-17 and 22-25 under 35 U.S.C. § 112, first paragraph on the grounds of non-enablement. The Examiner stated that the specification, "while being enabling for a solid, oral, controlled release dosage form comprising a pharmaceutically active ingredient having solubility in water of greater than 1gm in 250 mL water, and the said active ingredient is dispersed in a matrix, which provides the claimed release rate as tested by Ph. Eur. Basket method . . . , does not reasonably provide enablement for

achieving the claimed zero order release rate and specific release parameters using the same method with any type of matrix in which the active agent is dispersed." The Examiner further states that "absence any guidance one of ordinary skill in the art would have to perform undue experimentation so to optimize the combination of each and every active agent with every suitable matrix polymer that yields the claimed in vitro dissolution rate, when tested by the claimed method. Furthermore, . . ., a skilled artisan would not be able to achieve the same plasma concentrations, Tmax and Cmax values, as claimed, using any active agent, any matrix material and the specific method."

This rejection is respectfully traversed. It is well recognized that "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *United States v. Telectronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), cert. denied, 490 U.S. 8 USPQ2d at 1046 (1989). "The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art." *In re Wands*, 8 USPQ2d at 1404 *(citations omitted)*. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." Id. *(Emphasis added)*.

It is further submitted that Applicants are not required to exemplify every matrix formulation which would be encompassed by the claim. See, e.g., *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 84 (CCPA 1970); MPEP 2164.01(b) (8th Edition) ("As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied."). In *Telectronics*, for example, the court found that "[s]ince one embodiment is admittedly disclosed in the specification, along with the general manner in which

its current range was ascertained, we are convinced that other permutations of the invention could be practiced by those skilled in the art without undue experimentation." *Telectronics,* 8 USPQ2d at 1223 (*citing SRI Int'l v. Matsushita Elec. Corp. of America*, 775 F.2d 1107, 1121, 227 USPQ 577, 586 (Fed. Cir. 1985) (the law does not require an applicant to describe in his specification every conceivable embodiment of the invention)).

The art of pharmaceutical science requires both formulation work and clinical (in-vivo) evaluation, and giving due regard for the nature of the invention, it is respectfully submitted that the amount of experimentation required in order to obtain a pharmaceutical formulation which provides the claimed in-vitro and in-vivo parameters does not require undue experimentation.

The invention as claimed is directed to a solid, oral, controlled-release pharmaceutical dosage form comprising an active ingredient having the claimed solubility dispersed in a matrix, wherein the dosage form provides an essentially zero order rate of release of the pharmaceutically active ingredient over a period of 8 hours, the amount of the ingredient released over 8 hours being in the range of 15% to 45% (according to the claimed in-vitro testing), and further providing a median Tmax in the range of about 2.5 to about 6 hours and a ratio of mean Cmax to mean plasma level at 24 hours in a range of about 1.5 to 3.5 (according to the claimed in-vivo testing). The specification further exemplifies formulations which meet all of the claimed limitations.

At time the application was filed, numerous controlled release matrix technologies were well within the knowledge of pharmaceutical formulators having ordinary skill in the art. It is submitted that pharmaceutical formulators can manipulate these technologies, e.g., by varying the amount of controlled release carrier, in order to vary the in-vitro release rate.

Further, it is well known to those of ordinary skill in the art that upon formulating prospective products which might be useful in humans, in-vivo clinical studies must be conducted to determine whether the prospective product actually provides the desired in-vivo performance. Plasma profiles are routinely obtained during clinical trials and in particular during phase I-III studies as indicated in J.T. Cartensen, Pharmaceutical Principles of Solid Dosage Forms, 1993 (attached herewith).

It is respectfully submitted that none of the above steps, either separately or collectively, rise to the level of undue experimentation. Once the goal (the claimed in-vitro and in-vivo parameters) has been identified and attained (as demonstrated in the examples of the present specification), it is respectfully submitted that a pharmaceutical formulator of ordinary skill in the art can manufacture prospective dosage forms for evaluation (which meet, e.g., the claimed in-vitro parameters), a clinician of ordinary skill in the art can administer the dosage forms and draw blood at appropriate time intervals, and a pharmacokineticist of ordinary skill in the art can evaluate the blood plasma data. Based on the results, it is respectfully submitted that one skilled in the art could ascertain if the desired in-vitro and in-vivo parameters have been met, or could modify the formulation by routine experimentation (e.g., changing the matrix material) and submit the formulation to further routine testing.

Accordingly, it is submitted that one skilled in the art can make and use the invention commensurate in scope with the claims, based on routine experimentation and the Examiner is respectfully requested to remove the non-enablement rejection.

II. DOUBLE PATENTING REJECTION:

In the Office Action, the Examiner rejected claims 1-8 and 11-15 under the judicially created doctrine of obviousness type double patenting over claims 1-8 and 11-22 of U.S. Patent No. 6,399,096 and over claims 1-33 of U.S. Patent No. 5,965,163.

It is submitted that the filing of terminal disclaimers will be considered upon indication that the pending claims are otherwise allowable.

III. REJECTION UNDER 35 U.S.C. § 102(b):

In the Office Action, the Examiner rejected claims 1-4, 8, 11, 12, 14-17 and 23-25 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 4,828,836 (hereinafter "the Elger patent"). The Examiner stated that the "because Elger discloses claimed polymers of the matrix and also discloses various active agents (col. 3) that include the water soluble active agents . . . , the release rates claimed are inherent to the compositions."

This rejection is respectfully traversed. With respect to the rejection under the doctrine of inherency, it is noted that as set forth in the MPEP, 8th edition, section 2112, the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be recognized by one of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999).

It is further set forth in the MPEP, 8th edition, section 2112 that "[i]n relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the alleged inherent characteristic necessarily flows from the teachings of the applied prior art." Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. And Inter. 1990) (emphasis in original).

It is respectfully submitted that the claimed in-vitro and in-vivo parameters do not necessarily flow from the examples of the Elger reference. A stated above with respect to the non-enablement rejection, one skilled in the art can manipulate a formulation, e.g., by varying the amount of controlled release carrier, in order to vary the resultant parameters. Accordingly, other parameters other than the presently claimed parameters, can be obtained by the examples in Elger.

In fact, it is respectfully submitted that it has not been demonstrated that any of the exemplified compositions in the Elger reference meet all of the claimed in-vitro and in-vivo parameters. Accordingly, it is respectfully submitted that a *prima facie* case of anticipation based on inherency has not been established as the Examiner has not provided a basis in fact and/or technical reasoning to reasonably support the determination that the alleged inherent characteristic necessarily flows from the teachings of the applied prior art.

A check in the amount of $930.00 is enclosed for a three (3) month extension of time. It is believed that no other fees are due at this time. If it is determined that any additional fees are due or that any fees have been overpaid, the Commissioner for Patents is hereby authorized to charge said fees or credit any overpayment to Deposit Account No. 50-0552.

In view of the arguments presented, Applicants respectfully submit that the pending claims are in condition for allowance. An early and favorable Action on the merits is earnestly solicited.

Respectfully submitted,

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